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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

IN RE APPLICATION OF: GERONI Cristina et al.

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INTERNATIONAL APPLICATION NO.: PCT/EP00/00745

INTERNATIONAL FILING DATE: January 31, 2000

FOR: ANTITUMOUR SYNERGISTIC COMPOSITION

#4  
py  
12-6-57

**REQUEST FOR PRIORITY UNDER 35 U.S.C. 119**  
**AND THE INTERNATIONAL CONVENTION**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

<u>COUNTRY</u>	<u>APPLICATION NO</u>	<u>DAY/MONTH/YEAR</u>
Great Britain	9904387.9	25 February 1999

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/EP00/00745. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,  
OBLON, SPIVAK, McCLELLAND,  
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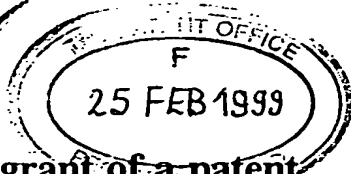
*Andrew Gensy*

Dated 13 October 1999

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# **Request for grant of a patent**

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form))

1. Your reference

P.76286 GCW.CMK

2. Patent application number

(The Patent Office will fill in this part)

**9904387.9**

**25 FEB 1999**

3. Full name, address and postcode of the or of each applicant (underline all surnames)

PHARMACIA & UPJOHN S.P.A.

Via Robert Koch 1.2  
20152 Milan  
Italy

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

Italy

7100001001

4. Title of the invention

ANTITUMOUR SYNERGISTIC COMPOSITION

5. Name of your agent (if you have one)

J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

14 SOUTH SQUARE  
GRAY'S INN  
LONDON WC1R 5LX

Patents ADP number (if you know it)

26001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number  
(if you know it)

Date of filing  
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer "Yes" if:

Yes

- a) any applicant named in part 3 is not an inventor, or
  - b) there is an inventor who is not named as an applicant, or
  - c) any named applicant is a corporate body:
- See note (d))

# Patents Form 1/77

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## Continuation sheets of this form

Description 6  
Claim(s) 2  
Abstract 1  
Drawing(s)

10. If you are also filing any of the following, state how many against each item.

## Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77) 2 x 5

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application

Signature

J A Kemp & Co

Date 25 February 1999

12. Name and daytime telephone number of person to contact in the United Kingdom Mrs C M Keen  
0171 405 3292

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## Notes

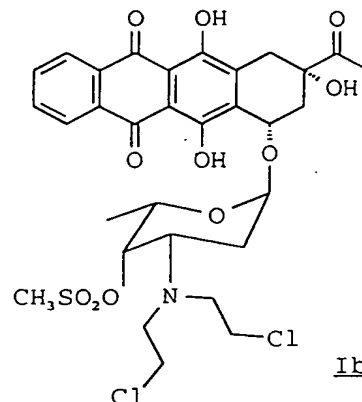
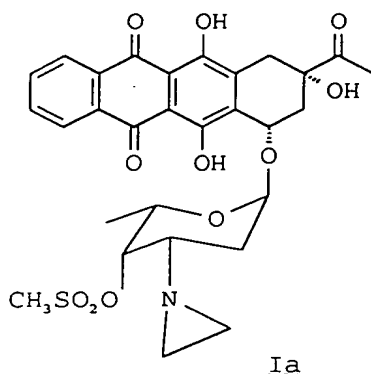
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### Antitumor Synergistic Composition

The present invention relates in general to the field of cancer treatment and, more particularly, provides an antitumor composition comprising an alkylating anthracycline and a  
 5 topoisomerase II inhibitor, having a synergistic or additive antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising

10 - an alkylating anthracycline of formula Ia or Ib :



- an antineoplastic topoisomerase II inhibitor, and a pharmaceutically acceptable carrier or excipient.

15 The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drug  
 20 Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,218 and US-A-5,496,800. Both compounds intercalate into DNA via the chromophore and alkylate guanine at N<sup>7</sup> position in DNA minor groove via their reactive moiety on position 3' of the amino sugar. Compounds Ia and Ib are able  
 25 to circumvent the resistance to all major classes of

cytotoxics, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

Topoisomerase II inhibitors are described in various scientific publications. The main representatives of this wide  
5 class of drugs are: the anthracycline derivatives such as doxorubicin, daunorubicin, epirubicin, nemorubicin and idarubicin; the podophyllotoxin compounds etoposide and teniposide; the anthraquinone derivative like mitoxantrone and amsacrine. See for example the review: Cancer, Principles and  
10 Practice of Oncology, Lippincott-Raven Ed. (1997), 452-467.

Doxorubicin and etoposide are the preferred topoisomerase II inhibitors to be used in the present invention. The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and an  
15 antineoplastic topoisomerase II inhibitor, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a  
20 neoplastic disease state comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and an antineoplastic topoisomerase II inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

25 The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combination preparation comprising an antineoplastic  
30 topoisomerase II inhibitor as defined above and an alkylating anthracycline of formula Ia or Ib, as defined above, in

amounts effective to produce a synergistic antineoplastic effect.

By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a topoisomerase II inhibitor to mammals, including human.

By the term "administered " or "administering" as used herein

is meant parenteral and /or oral administration. By

"parenteral" is meant intravenous, subcutaneous and intramuscular administration. In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the compound with the topoisomerase II

inhibitor activity, for example of the anthracycline or etoposide class, or the compounds may be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according to, inter alia, the particular formulation of the alkylating anthracycline of formula Ia or Ib being utilized, the particular formulation of the topoisomerase II inhibitor, such as one of the anthracycline or etoposide class, being utilized, the particular tumor model being treated, and the particular host being treated.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib, the course of therapy generally employed is from about 0.1 to about 200 mg/m<sup>2</sup> of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m<sup>2</sup> of body surface area.

In the method of the subject invention, for the administration of the topoisomerase II inhibitor the course of therapy

generally employed is from about 1 to about 1000 mg/m<sup>2</sup> of body surface area. More preferably, the course therapy employed is from about 10 to about 500 mg/m<sup>2</sup> of body surface area. The antineoplastic therapy of the present invention is in

5 particular suitable for treating breast, ovary lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to the preparation of a pharmaceutical composition containing an  
10 effective amount of an alkylating anthracycline of formula Ia or Ib as defined above and an antineoplastic topoisomerase II inhibitor in the prevention or treatment of metastasis or for the treatment of tumors by angiogenesis inhibition, as well as to the use of an alkylating anthracycline of formula Ia or Ib  
15 as defined above and an antineoplastic topoisomerase II

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inhibitor for the treatment of tumors by angiogenesis inhibition or for the treatment or prevention of metastasis . As stated above, the effect of an alkylating anthracycline of formula Ia or Ib and a topoisomerase II inhibitor, such as an  
20 anthracycline or etoposide derivative, is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline and of the topoisomerase II inhibitor and thus yields the most  
25 effective and least toxic treatment for tumors. The superadditive actions of the combination preparation of the present invention are shown for instance by the following in vivo tests, which are intended to illustrate but not to limit the present invention.

30 Table 1 shows the antileukemic activity on disseminated L1210 murine leukemia obtained combining Ia with etoposide. At the dose of 30 mg/kg of etoposide alone (day +3) and at the dose

of 1 mg/kg of Ia alone (days +1,2) were associated, without toxicity, with ILS% values of 100 and 67, respectively.

Combining etoposide and Ia at the same doses with the same schedule an increase of activity with ILS% values of 450 was observed, indicating a synergistic effect.

Table 2 shows the antileukemic activity on disseminated L1210 murine leukemia obtained combining Ia with doxorubicin. At the dose of 13 mg/kg of doxorubicin alone (day +3) and at the dose of 1.5 mg/kg of Ia alone (days +1,2) were associated, without toxicity, with ILS% values of 50 and 67, respectively. Combining doxorubicin and Ia at the same doses with the same schedule an increase of activity with ILS% values of 150 was observed, indicating a synergistic effect.

For these experiments Ia was solubilized in [Cremophor® /EtOH= 6.5:3.5]/[normal saline]=20/80 v/v, while standard etoposide pharmaceutical preparation and doxorubicin solubilized in water were used.

Table 1: Antileukemic activity against disseminated L1210<sup>1</sup> murine leukemia of Ia in combination with Etoposide

Compound	Treatment schedule	Dose <sup>2</sup> (mg/kg/day)	ILS% <sup>3</sup>	Tox <sup>4</sup>	LTS <sup>5</sup>
Ia	iv +1,2	1	67	0/10	0/10
Etoposide	iv +3	30	100	0/10	0/10
Ia + Etoposide	iv +1,2 iv +3	1 + 30	450	0/10	4/10

Table 2: Antileukemic activity against disseminated L1210<sup>1</sup> murine leukemia of Ia in combination with Doxorubicin

Compound	Treatment schedule	Dose <sup>2</sup> (mg/kg/day)	ILS% <sup>3</sup>	Tox <sup>4</sup>	LTS <sup>5</sup>
Ia	iv +1,2	1.5	67	0/10	0/10
Doxorubicin	iv +3	13	50	0/10	0/10
Ia + Doxorubicin	iv +1,2 iv +3	1.5 + 13	150	0/10	3/10

1) L1210 leukemia cells (10<sup>5</sup>/mouse) are injected iv on day 0.

2) Treatment is given starting on day 1 after tumor transplantation (day 0).

3) Increase in life span: [(median survival time of treated mice/median survival time of controls) x 100] - 100

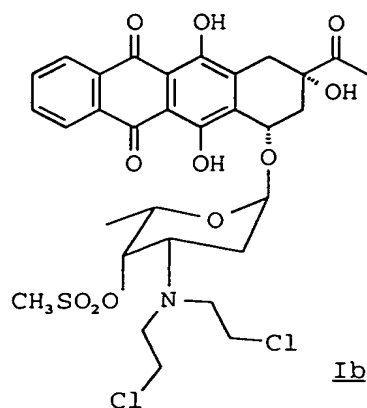
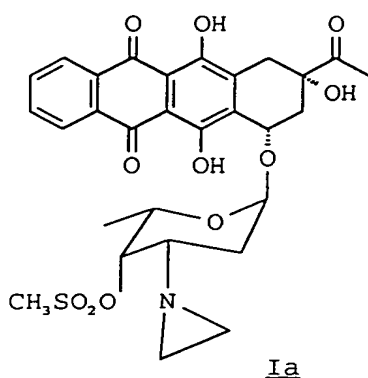
4) Number of toxic deaths/number of mice.

5) Long Term Survivors (>60 days) at the end the experiment.

## Claims

1. Products containing an alkylating anthracycline of formula Ia or Ib:

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and an antineoplastic topoisomerase II inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

10 2. Products according to claim 1 wherein the alkylating  
anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-  
methansulfonyl daunorubicin.

3. Products according to claim 1 or 2 wherein the topoisomerase II inhibitor is etoposide.

15 4. Products according to claim 1 or 2 wherein the  
topoisomerase II inhibitor is doxorubicin.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in

20 claim 1 and an antineoplastic topoisomerase II inhibitor.

6. A composition according to claim 5 wherein the topoisomerase II inhibitor is doxorubicin or etoposide.

7. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antineoplastic topoisomerase II

inhibitor in the preparation of a medicament for use in the treatment of tumors.

8. Use according to claim 7 wherein the topoisomerase II inhibitor is etoposide or doxorubicin.

- 5 9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and an antineoplastic topoisomerase II inhibitor in the preparation of a medicament for use in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

## ABSTRACT

## Antitumor Synergetic Composition

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There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and an antineoplastic topoisomerase II inhibitor in the treatment of tumors and the use of said combination in the treatment or prevention of metastasis or in the treatment of tumors by inhibition of angiogenesis.

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